PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 59.80151/002	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/GB2004/002779	International filing date *(day/month/year)* 25 June 2004 (25.06.2004)	Priority date *(day/month/year)* 25 June 2003 (25.06.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant UNITARGETING RESEARCH AS		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 13 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 03 January 2006 (03.01.2006)
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/002779	25.06.2004	25.06.2003

International Patent Classification (IPC) or both national classification and IPC
C12N15/62, C12N15/63, C12N9/02, C07K19/00, C12N5/10, C12P21/02

Applicant
UNITARGETING RESEARCH AS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ The International Searching Authority has not been able to consider the validity of the priority claim because a copy of the earlier application whose priority has been claimed was not available to the International Searching Authority at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 27 (partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 27 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
☐ has not been furnished
☐ does not comply with the standard

the computer readable form
☐ has not been furnished
☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-26,28,29 (completely), 27 (partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7-9,14,20,21,24-29
	No:	Claims	1-6,10-13,15-19,22,23
Inventive step (IS)	Yes:	Claims	14
	No:	Claims	7-9,20,21,24-29
Industrial applicability (IA)	Yes:	Claims	1-29
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. No search report has been established for the subject-matter of invention II (see item IV below). Consequently, this written opinion is given on the subject-matter of invention I, namely, claims 1-26, 28, 29 (completely) and claim 27 (partially)

Re Item IV

Lack of unity of invention

1. This Authority considers that there are 2 inventions covered by the claims of the present application indicated as follows:

   I: Claims 1-26, 28, 29 (completely) and claim 27 (partially) directed to a method of producing a target protein using nucleic acids which encode a chimaeric protein comprising a signal peptide from a non-mammalian bulk-secreted protein and said target protein; a nucleic acid encoding said chimaeric protein; a vector comprising said nucleic acid; a host cell comprising said nucleic acid or said vector; a method of obtaining a target protein using said host cells; a kit comprising said vector and said cell.

   II: Claim 27 (partially) directed to a method of producing a target protein using nucleic acids which encode a chimaeric protein comprising a signal peptide from a mammalian bulk-secreted protein and said target protein.

2. Consequently, the present application does not satisfy the criterion set forth in Rule 13.1 PCT (unity of invention).

3. The claims of the present application relate to methods of producing target proteins using nucleic acids which encode a chimaeric protein comprising a signal peptide from a bulk-secreted protein and said target protein.

4. In assessing whether the requirements of unity of invention of an application are met, identification of the technical features that each solution to a technical problem contributes over the prior art (special technical features) must be made. If then a

technical relationship between the solutions, involving one or more of the same special technical features, can be recognised, the requirements of unity of invention are said to be met.

5. Regarding the prior art, WO 02/46430 describes the production of IL-18BP using a nucleic acid encoding a chimaeric protein comprising IL-18BP and the signal peptide from the human growth hormone, a mammalian bulk-secreted protein.

6. Therefore, in light of prior art, and since claim 27 is not restricted to non-mammalian bulk-secreted proteins, the problem identified in the present application can be considered as the provision of further methods of producing target proteins using nucleic acids which encode a chimaeric protein comprising a signal peptide from a bulk-secreted protein and said target protein.

   The first solution 1 to this problem is given by claims 1-26, 28, 29 (completely) and 27 (partially): a method of producing a target protein using nucleic acids which encode a chimaeric protein comprising a signal peptide from a non-mammalian bulk-secreted protein and said target protein; a nucleic acid encoding said chimaeric protein; a vector comprising said nucleic acid; a host cell comprising said nucleic acid or said vector; a method of obtaining a target protein using said host cells; a kit comprising said vector and said cell.

   The second solution to this problem is given by claim 27 (partially): a method of producing a target protein using nucleic acids which encode a chimaeric protein comprising a signal peptide from a mammalian bulk-secreted protein and said target protein.

7. As no technical features can be distinguished which, in the light of the prior art, could be regarded as special technical features on which an unifying concept could be based, there is no single inventive concept underlying the plurality of claimed inventions of the present application.

   Therefore, an objection to lack of unity of invention has to be raised under Rule 13.1 PCT. Consequently, a distinction of separate inventions has been made (I-II), based

on technical features. The resulting separate inventions, as presently identified, have been grouped according to the order in which they have been claimed.

8. The applicant is informed that it an objection under Rule 13.1 PCT could also be raised against the subject-matter of invention I, namely that the luciferase signal peptides from *Gaussia princeps* and *Vargula hilgendorfii* constitute separate inventions. The underlying unifying concept between the *Gaussia princeps* and *Vargula hilgendorfii* luciferase signal peptides is their use in the production of target proteins. Documents D1 and D2 of the International Search Report disclose the use of the *Vargula hilgendorfii* luciferase signal peptide to direct the membrane translocation of a chimaeric protein comprising luciferase and synaptotagmin-I. Therefore, since the *Vargula hilgendorfii* luciferase signal peptide has been demonstrated in the art to translocate chimaeric proteins, the use of said signal peptide in a method of producing target proteins is considered to be obvious to the skilled person and, therefore, not inventive (Article 33(3) PCT: see item V 3 below). Also, It should be noted that claims 1-6 do not exclude the presence of the native luciferase protein in the claimed method. Consequently, the underlying unifying concept between the *Gaussia princeps* and *Vargula hilgendorfii* luciferase signal peptides is not considered to be inventive and, as a result, each signal peptide should be regarded as a separate invention.

However, for the purpose of convenience, this written opinion is directed to the subject-matter of invention I which includes both the *Gaussia princeps* and *Vargula hilgendorfii* luciferase signal peptides.

Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Citations

1.1 The documents mentioned in the present written opinion are numbered as in the International Search Report i.e. D1 corresponds to the first document of the search report etc.

2. Novelty (Article 33(2) PCT)

2.1 The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject matter of claims 1-6, 10-13, 15-19, 22 and 23 is not new in respect to the prior art as defined in the regulations (Rule 64(1)-(3) PCT).

2.2 Documents D1 and D2 both describe a method of producing a chimaeric protein by fusing the C-terminus of the *Cypridina (Vargula) hilgendorfii* luciferase fused to the N-terminus of synaptotagmin-I. The hybrid protein uses the luciferase signal peptide for membrane translocation. D1 and D2 also discloses the nucleic acid encoding the chimaeric protein, a vector comprising said nucleic acid, and mammalian host cells comprising said vector. Consequently, D1 and D2 appear to be novelty destroying for the subject-matter of claims 1-6, 10-13, 15-19, 22 and 23 (Article 33(2) PCT).

2.3 The use of the *Gaussia princeps* signal peptide in a method of producing a heterologous target protein does not appear to be disclosed in the prior art and therefore, the subject-matter of claims 1-29, with regards to only the *Gaussia princeps* signal peptide, appears to meet the requirements of Article 33(2) PCT.

3. Inventive step (Article 33(3) PCT)

3.1 The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject matter of claims 7-9, 20, 21 and 24-29 does not involve an inventive step (Rule 65(1)(2) PCT).

3.2 Documents D1 and D2, which are considered to be the closest prior art to the subject-matter of claim 7, disclose a method of producing a chimaeric protein by fusing the C-terminus of the *Vargula hilgendorfii* luciferase fused to the N-terminus of synaptotagmin-I whereby the luciferase signal peptide is employed for membrane translocation. The difference between D1 and D2 and the subject-matter of claim 7 is that the applicants remove most of the luciferase protein in the chimaeric construct. The technical effect of this difference is that only a target protein is produced and secreted. The apparent technical problem can therefore be considered as to provide a method of producing and secreting only a target protein. It was known in the art that the *Vargula hilgendorfii* luciferase protein comprised a signal peptide for secretion and, furthermore, its functionality had been demonstrated (D1, D2). Therefore, in

order to overcome the apparent technical problem the skilled person would merely have to engineer a chimaeric protein comprising the known *Vargula hilgendorfii* luciferase signal peptide and a desired target protein. The skilled person would be able to do this with a reasonable expectation of success using techniques which are routine in the field of molecular biology. Thus, the subject-matter of claim 7 does not appear to be inventive (Article 33(3) PCT).

3.3 The same objections stated in item 3.2 above are also applicable *mutatis mutandis* to the subject-matter of independent claims 20, 25, 26 and 27 (Article 33(3) PCT).

3.4 Dependent claims 8, 9, 21, 24, 28 and 29 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, see documents D1 and D2 and the corresponding passages cited in the International Search Report.

3.5 Regarding the *Gaussia princeps* luciferase signal peptide the use of this signal peptide in a method to produce a heterologous protein appears to be neither disclosed nor suggested by the prior art and, therefore, the subject-matter of claims 1-29, as far as the *Gaussia princeps* luciferase signal peptide is concerned, appears to meet the requirements of Article 33(3) PCT. The subject-matter of claim 14 appears to be, in any case, both novel (Article 33(2) PCT) and inventive (Article 33(3) PCT) since the subject-matter of said claim is restricted to the *Gaussia princeps* luciferase signal peptide.

4. Industrial applicability (Article 33(4) PCT)

4.1 The subject-matter of claims 1-29 has industrial applicability (Article 33(4) PCT).

Re Item VII

Certain defects in the international application

1. Claims 1-11, 15, 16, 19, 20-27 and 29 are neither sufficiently disclosed nor supported by the description as is required by Articles 5 and 6 PCT. Said claims refer to all non-mammalian bulk-secreted protein signal peptides (see also item VIII below) whereas the application only discloses, in the sense of Article 5 PCT, and supports, in the

sense of Article 6 PCT, a limited number of signal peptides, namely, the signal peptides from the *Gaussia princeps* and *Vargula hilgendorfii* luciferases.

2. The claims of the present application refer to the organism *Guassia princeps* when they should, in fact, refer to *Gaussia princeps*.

Re Item VIII

Certain observations on the international application

1. The term "bulk-secreted protein" used in claims 1, 20 and 27 and "variant(s) or fragments thereof" used in claims 14, 17 and 18 are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.